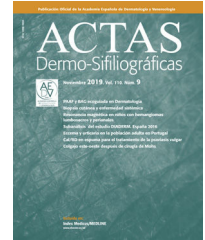




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PRACTICAL DERMATOLOGY

[Translated article] Mucocutaneous Alterations After Hematopoietic Stem Cell Transplantation: Literature Update and Review



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KEYWORDS

Hematopoietic stem cell transplantation;
Allogeneic transplant;
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Skin cancer

Abstract In recent years, hematopoietic stem cell transplantation (HSCT) has revolutionized the treatment of various hematological and non-hematological diseases. Its implementation is not stranger to risks and involves a significant rate of complications, including mucocutaneous adverse events. We present a narrative review of the mucocutaneous alterations observed after HSCT. Among these, acute and chronic graft-versus-host disease (GVHD) stand out, whose diagnosis and treatment can be challenging. Other common conditions include cutaneous adverse reactions and infections with mucocutaneous involvement. Additionally, various studies indicate that these individuals may have a higher rate of mucocutaneous neoplasms. Early identification and management of these complications, along with a multidisciplinary approach, are essential to improving these patients' quality of life and long-term outcomes. Furthermore, it is advisable to screen for skin cancer in these individuals, especially if they have other associated risk factors.

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PALABRAS CLAVE

Trasplante de progenitores hematopoyéticos;
Trasplante alogénico;
Trasplante autólogo;

Alteraciones mucocutáneas tras trasplante de progenitores hematopoyéticos: revisión y actualización de la literatura

Resumen En los últimos años, el trasplante de progenitores hematopoyéticos (TPH) ha revolucionado el tratamiento de diversas enfermedades hematológicas y no hematológicas. Su realización no está exenta de riesgos y conlleva una tasa significativa de complicaciones, entre ellas mucocutáneas. Presentamos una revisión narrativa de las alteraciones mucocutáneas

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Enfermedad injerto contra huésped; Cáncer cutáneo

observadas tras TPH. Entre ellas, destacan la enfermedad de injerto contra receptor (EICR) aguda y crónica, cuyo diagnóstico y tratamiento pueden ser notoriamente complejos. Otras patologías frecuentes son las toxicodermias y las infecciones con afectación mucocutánea. Además, diversos estudios muestran que estos individuos pueden tener una mayor tasa de neoplasias mucocutáneas. La identificación y manejo temprano de estas complicaciones, junto con un enfoque multidisciplinar, son esenciales para mejorar la calidad de vida y los resultados a largo plazo de estos pacientes. Asimismo, es recomendable el cribado de cáncer cutáneo en estos individuos, especialmente si presentan otros factores de riesgo.

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Introduction

Hematopoietic stem cell transplantation (HSCT), which includes bone marrow, peripheral blood, and umbilical cord blood transplants, involves administering healthy hematopoietic stem cells to patients with dysfunctional bone marrow due to malignant hematological diseases, bone marrow failure syndromes, or severe immunodeficiencies. HSCT can be autologous or allogeneic, depending on whether the hematopoietic cells come from the patient or a donor, respectively. Currently, HSCT is established as the treatment of choice for various severe malignant and non-malignant hematological conditions.¹ According to data from the Spanish National Transplant Organization (ONT), more than 3500 HSCTs were performed in 2022—double the number conducted in 2002.²

HSCT includes a conditioning phase, in which chemotherapy and/or radiotherapy is administered to prepare the recipient's bone marrow and eliminate neoplastic cells (Fig. 1). One or two days later, the infusion phase is conducted. The patient then enters the aplasia period, during which immunity is significantly reduced due to lack of blood cell production by the bone marrow. This is a critical stage, during which the patient may experience severe anemia, bleeding, and infections. Finally, the engraftment phase occurs, beginning when the transplanted stem cells start producing new cells in the marrow. The time to engraftment varies depending on the type of transplant and patient-specific conditions, ranging from 11 to 40 days.³

After HSCT, patients may experience numerous mucocutaneous complications resulting from the transplant itself, the immunosuppressive therapy, or the graft-versus-host effect. A recent study reported that up to 45% of HSCT recipients developed some type of skin eruption within year 1 after receiving the transplant, with rates rising to 60–70% in the long term. These complications can significantly impact patients' quality of life and may even be life-threatening.⁴ This article reviews the mucocutaneous changes observed in HSCT recipients, focusing on acute and chronic graft-versus-host disease (GVHD), drug eruptions, infections, and mucocutaneous neoplasms.

Graft-versus-host disease after hematopoietic stem cell transplantation

In GVHD, the immune cells from the graft (transplant) recognize the recipient (patient) as foreign and attack their

tissues. GVHD is categorized into acute (aGVHD) and chronic (cGVHD) forms. Classically, they were differentiated by timing (before or after day 100 post-HSCT), but current classification is based on different pathophysiologic mechanisms and clinical presentations (Table 1).^{5–7} GVHD can affect any organ, although skin and mucous membranes are most widely involved (20–70%), and this involvement often aids diagnosis. It is an intrinsic complication of allogeneic HSCT (allo-HSCT), where donor cells differ from the recipient's, which significantly contributes to morbidity and mortality, being the most common cause of death after hematologic malignancy relapse.⁶

Acute graft-versus-host disease

aGVHD frequently first affects the skin and mucous membranes. The liver and intestines are typically affected next. The classic aGVHD triad includes skin rash, hyperbilirubinemia, and diarrhea. Traditionally, it appears and resolves within the first 100 days post-HSCT (often developing between days 30–40). However, it may also occur later (late onset), persist beyond 100 days, or recur after resolution.⁷ It is graded into 4 stages: grade 1 (+): <25% of total body surface area (TBSA) involved; grade 2 (++): 25–50% TBSA; grade 3 (+++): 50–75% TBSA; grade 4 (++++): >75% TBSA.⁷ Cutaneous presentation (Fig. 2) typically begins with dysesthesias, pruritus, erythema, or edema, progressing into a morbilliform rash, often folliculotropic and trunk-predominant, then becoming confluent and spreading centrifugally. Palmar, plantar, and retroauricular involvement is a typical finding as well. Severe cases may develop epidermal detachment and blistering. The oral, genital, nasal, and ocular mucosa may also be involved, presenting as mucositis.⁸

Initial suspicion of aGVHD is based on clinical findings: the triad of rash, diarrhea, and hyperbilirubinemia—although not all signs may be present or other organs may be affected. Skin biopsy is not pathognomonic. Histologically, aGVHD can be categorized into grade I: focal vacuolar changes at the basal membrane, with sparse lymphocytic infiltrate; grade II: keratinocyte necrosis with more evident vacuolar damage; grade III: keratinocyte apoptosis, dermoepidermal junction obliteration, lichenoid dermal infiltrate; grade IV: total epidermal necrosis with dermoepidermal separation.⁹

Differential diagnosis is complex (Table 2, Fig. 2). Rashes due to drug eruptions or viral infections may mimic aGVHD. In this context, concurrent diarrhea and hyper-

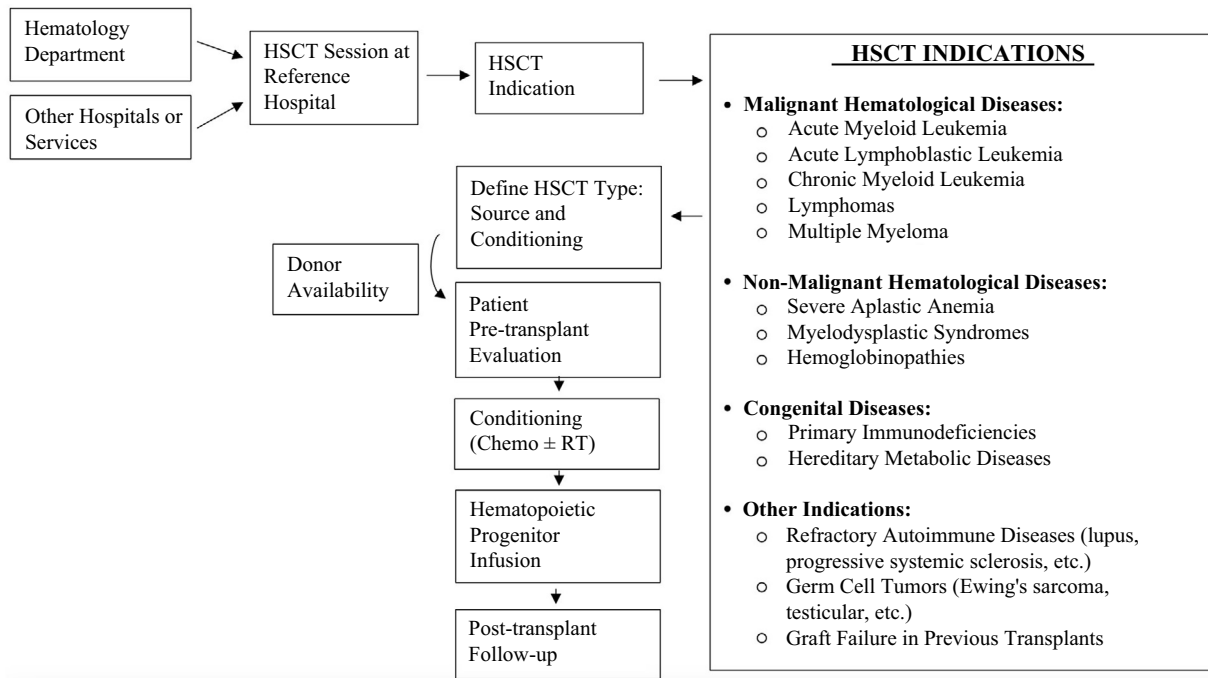


Figure 1 Indications and process of HSCT. Chemo: chemotherapy; RT: radiotherapy; HSCT: hematopoietic stem cell transplantation.

Table 1 GVHD classification.

Type		Time since HSCT	Acute GVHD signs/symptoms ^a	Chronic GVHD signs/symptoms ^b
Acute GVHD	Classic	≤100 days	+	—
	Persistent, recurrent, or late-onset	>100 days	+	—
Chronic GVHD	Classic lichenoid	No time limit, typically earlier	—	+
	Classic sclerodermiform	No time limit, typically later	—	+
	Other patterns of chronic GVHD	Variable	—	+
Overlap syndrome	—	—	+	+

Source: Adapted from Jagasia et al.⁵ and Ballester-Sánchez et al.⁷

GVHD: graft-versus-host disease; HSCT: hematopoietic stem cell transplantation.

^a Acute GVHD signs/symptoms: maculopapular rash, diarrhea, cholestatic hepatitis.

^b Chronic GVHD signs/symptoms: skin: sclerodermiform, lichenoid, or other patterns; mouth: dry syndrome, lichenoid, erosive, etc.; genital: dry syndrome, lichenoid, erosive, etc.; gastrointestinal: chronic diarrhea, abdominal pain, hepatic dysfunction; pulmonary: bronchiolitis obliterans; muscular, joint, neurological: peripheral or central neuropathy, etc.

bilirubinemia support the diagnosis of aGVHD; a new drug exposure supports drug eruption; and respiratory symptoms or PCR/serologic positivity support infection.^{5,8,10} Histologically, sparse eosinophils and absence of spongiosis in aGVHD may help distinguish it from drug eruptions.^{11,12} Similarly, immunohistochemical markers such as elafin¹³ and more recently, microRNA expression,¹⁴ have been proposed for aGVHD diagnosis, but validation is ongoing and diagnosis may remain uncertain despite thorough work-up.

The treatment of aGVHD depends on the grade and location of the disease. For localized grade I cutaneous aGVHD, topical corticosteroids may be used. In grade II aGVHD, sys-

temic treatment with corticosteroids such as prednisone (1–2 mg/kg/day, although lower doses may be sufficient) is required. For corticosteroid-refractory cutaneous aGVHD, a therapeutic option is extracorporeal photopheresis, which achieves complete response rates >80%, improves survival, and reduces mortality—especially when initiated within the first 35 days. UVA-1 and UVB phototherapy can also be beneficial in localized skin signs. Another alternative in refractory cases is the use of antithymocyte globulin (ATG). Among pharmacologic treatments, tacrolimus, mycophenolate mofetil, sirolimus, and Janus kinase inhibitors (JAK inhibitors), particularly ruxolitinib,^{15,16} are notable. The

Table 2 Differential diagnosis of mucocutaneous signs of acute GVHD.^a

Differential diagnosis	Key clinical clues	Additional tests
Drug eruptions	Triggering drug exposure; absence of other suggestive GVHD symptoms. ^b Atypical targets or epidermal detachment (SJS/TEN). Lymphadenopathy and facial edema (DRESS). Pustules and fever (AGEP). Retroauricular, folliculotropic trunk, or palmoplantar involvement favors GVHD.	Histology: absence of adnexal involvement, presence of spongiosis and dermal eosinophils favors drug eruptions, though not specific. Lab test results: elevated liver enzymes, renal or cardiac dysfunction suggest DRESS; neutrophilia suggests AGEP; cholestatic liver pattern suggests GVHD.
Viral exanthem	More common in children; associated cough, conjunctivitis, rhinorrhea, reactive lymphadenopathy; typically non-pruritic; absence of other GVHD signs.	Viral serologies, viral PCR.
Engraftment syndrome	Occurs within the first 2 weeks post-HSCT (including autologous transplants). Common features include fever, pulmonary edema, weight gain, absence of diarrhea.	Lab test results: absence of transaminitis supports engraftment syndrome.
Connective tissue autoimmune diseases (e.g., lupus, dermatomyositis, morphea, systemic sclerosis)	Signs/symptoms of lupus (mucocutaneous, joint, muscle, lung, neuropsychiatric, etc.), dermatomyositis (cutaneous, muscle), morphea (indurated plaques, usually with prior inflammatory violet halo, without HSCT history), systemic sclerosis (scleroderma, Raynaud, digital ulcers, telangiectasias, calcinosis, musculoskeletal, dysphagia, lung involvement). Absence of other GVHD signs.	Lab test results: autoantibodies may be present. Muscle enzyme elevation in dermatomyositis.
Contact dermatitis	History of exposure to irritant/allergen, prior sensitization, sharply demarcated lesions, pruritus, absence of other GVHD signs.	Patch testing in allergic contact dermatitis.
Psoriasis	Well-defined erythematous-squamous plaques, Auspitz sign, predominance on extensor surfaces, scalp involvement, joint manifestations, and absence of other signs of GVHD.	Characteristic histology in psoriasis.
Lichen planus	Violaceous, pruritic, polygonal papules, often on wrists and ankles; Wickham striae; absence of GVHD signs.	Characteristic histology in lichen planus.
Zinc deficiency	Acral, periorificial dermatitis and alopecia; history of poor diet, alcoholism, or GI disease; improves with zinc supplementation; absence of GVHD signs.	Lab tests: serum zinc and alkaline phosphatase levels.

Source: Adapted from the authors' original work.

DRESS: Drug Reaction with Eosinophilia and Systemic Symptoms; GVHD: graft-versus-host disease; AGEP: Acute Generalized Exanthematous Pustulosis; SJS/TEN: Stevens–Johnson Syndrome/Toxic Epidermal Necrolysis; HSCT: hematopoietic stem cell transplantation.

^a Retroauricular, palmoplantar, and folliculotropic trunk involvement are highly characteristic in suspected acute GVHD. Diarrhea or hyperbilirubinemia on lab testing may aid diagnosis.

^b Some drug eruptions such as DRESS may also cause liver involvement and fever with multiple organ features—patient context must always be evaluated holistically.

latter has recently been approved for steroid-refractory aGVHD.¹⁷

Chronic graft-versus-host disease

cGVHD is a multisystem disease potentially affecting any organ, with skin and oral mucosa being the most commonly

involved sites—up to 80% of cases. Other affected organs include liver, eyes (dry eye syndrome), gut, and lungs. Musculoskeletal and psychological involvement is also common due to the chronicity of the disease.^{5,10,18,19}

Mucocutaneous cGVHD is polymorphic, affecting skin, oral, and genital mucosa (Table 3, Fig. 3). In 2014, the NIH Consensus Project proposed an organ-specific classification of cGVHD.^{5,7}

Table 3 Clinical signs of mucocutaneous chronic GVHD.

Skin	Hair	Nails	Oral mucosa	Genital mucosa
Lichen planus-like	New-onset alopecia	Roughness	Keratotic plaques,	Lichen planus-like
Lichen sclerosus-like	(especially patchy >	Thinning Breakage	lichen planus-like	lesions Vulvovaginal
Morphea-like	diffuse).	Fragility	lesions	stenosis or scarring
Fasciitis-like	Can be scarring or	Onycholysis	Microstomia due to	Fissures
Poikiloderma	non-scarring	Dorsal pterygium	sclerosis Gingivitis	Erosions
Psoriasiform	Premature gray hair	Anonychia	Mucositis,	Ulcers
Eczematous/dyshidrotic	discoloration		Pseudomembranes	Balanitis
SCLE-like			Ulcers	Phimosis
Pityriasis rosea-like			Xerostomia	
Ichthyosiform/keratosis			Mucosal atrophy	
pilaris-like			Mucocele	
Hypopigmentation				
Hyperpigmentation				
Vitiligo				
Angiomatoid nodules				
Calcinosis cutis				

Source: Own elaboration.
GVHD: graft-versus-host disease; SCLE: Subacute Cutaneous Lupus Erythematosus.
The "diagnostic" criteria from the NIH Consensus Project are highlighted in bold. These criteria refer to cutaneous signs that are sufficient for making a clinical diagnosis of chronic GVHD. The remaining criteria are referred to as "distinctive" for chronic GVHD, as they require the exclusion of other possible etiologies.

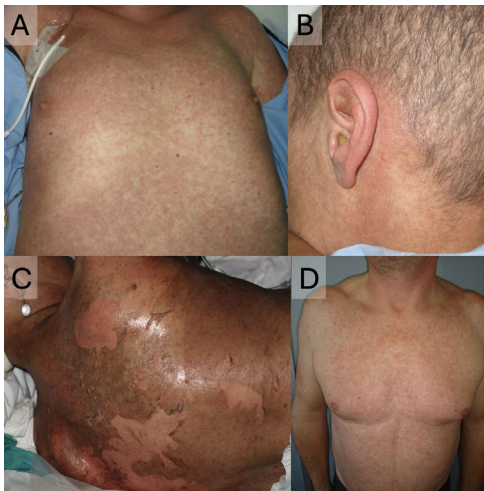


Figure 2 Acute cutaneous GVHD. A. Maculopapular rash affecting the trunk, with follicular predominance. B. Retroauricular involvement, characteristic of the disease. C. Epidermal detachment in a patient with grade 4 aGVHD. D. Maculopapular rash affecting the trunk, with follicular predominance. This patient was ultimately diagnosed with a piperacillin-tazobactam-induced drug eruption. Note the diagnostic challenge with GVHD, as this case is very similar to patient A.

Diagnosis is clinical and may be supported by skin biopsy. Histologically, 2 major patterns are recognized: lichenoid pattern: acanthosis, orthokeratotic and parakeratotic hyperkeratosis, band-like lymphocytic infiltrate, basal vacuolization, apoptotic keratinocytes, similar to lichen planus but with satellite cell necrosis. Sclerodermiform pattern: dermal sclerosis and periadnexal fat loss, resembling morphea or lichen sclerosus. Less common variants



Figure 3 Chronic mucocutaneous GVHD. A-C. Lichen planus-like pattern affecting the back (A), labial and buccal mucosa (B), and tongue (C). D. Nail involvement with onycholysis and pterygium formation. E. Scleroderma-like pattern with secondary hyperpigmentation. F. Fasciitis-like pattern. G. Genital mucosa involvement with sclerodermiform, lichen sclerosus-like changes. H. Poikiloderma-like pattern. I. Lichen sclerosus-like pattern with extragenital involvement on the back. J. Keratosis pilaris-like pattern. K. Psoriasiform pattern.

include fascial and psoriasiform patterns.^{9,20} These findings are nonspecific and must be interpreted clinically. Biomarkers for cGVHD are under investigation.²¹ Differential diagnoses include aGVHD, drug eruptions, viral infections, lichen planus, psoriasis, morphea, and systemic sclerosis.^{5,7}

Regarding the treatment of mucocutaneous cGVHD, standardized therapeutic clinical practice guidelines are lacking, as most clinical trials exclude dermatologic outcomes. Proper skin care is essential, including general measures and emollients. First-line therapy for mild forms includes topical corticosteroids. Topical calcineurin inhibitors may be used as corticosteroid-sparing agents. In more severe cases, phototherapy (UVB or UVA1), extracorporeal photopheresis, rituximab, imatinib (especially in sclerodermiform forms), and more recently, ibrutinib and ruxolitinib^{10,15,16} are widely used. For oral and genital involvement, treatment is similar, with particular benefit noted from tacrolimus mouth rinses for oral lichenoid lesions.²² A multidisciplinary follow-up approach (hematology, dermatology, rheumatology, gynecology, among others) is essential given the chronicity of this disease and its potential complications.

Skin cancer after hematopoietic stem cell transplantation

Chronic immunosuppression is clearly associated with skin cancer in solid organ transplant (SOT) recipients.^{23–27} However, the relationship between HSCT and skin cancer is less well documented. HSCT recipients have an increased risk of secondary malignancies vs the general population.^{28–30} Solid tumors develop in up to 15% of patients 15 years after HSCT with myeloablative conditioning and account for 5–10% of late deaths.³⁰ Regarding skin cancer (Table 4),^{29,32,50,52–61,65–67} published studies reveal an approximate incidence of 1–2% at the 5-year follow-up, 1–7% at the 10-year follow-up, and 6–10% at the 20-year follow-up.³³ Several risk factors have been identified, including male sex, age at the time of HSCT, prior history of skin cancer, conditioning regimen, total body irradiation (TBI), use of voriconazole for antifungal prophylaxis, and presence of cGVHD.^{29–33} A recent systematic review and meta-analysis reported a standardized incidence ratio (SIR) for post-HSCT skin cancer of 7.21 (95%CI, 3.98–13.08), with an SIR of 2.25 (95%CI, 1.7–3.68) for autologous HSCT and 10.18 (95%CI, 5.07–20.43) for allogeneic HSCT. Risk factors for skin cancer included cGVHD—specifically for basal cell carcinoma and cutaneous squamous cell carcinoma (cSCC)—as well as male sex and voriconazole exposure for cSCC.³⁴ GVHD, particularly cGVHD with mucocutaneous involvement, may be associated with increased skin cancer risk for several reasons: chronic inflammation of the skin and mucosa in cGVHD patients, and the greater need for immunosuppression in its treatment. Chronic inflammation has already been demonstrated to be an independent risk factor for skin cancer, particularly cSCC.⁴⁹ Furthermore, voriconazole is a well-known phototoxic and carcinogenic drug, linked to the production of reactive oxygen species during its metabolism. Its use as antifungal prophylaxis in HSCT patients has been

associated with skin cancer, particularly within the actinic keratosis–cSCC spectrum.^{50–52}

Due to the increased risk of skin cancer, several authors have recommended selective screening and ongoing dermatologic surveillance in these patients.^{34–36}

Other mucocutaneous alterations after HSCT (Table 5)^{37,41–44,45,47,50,70}

Patients who undergo HSCT may present with numerous mucocutaneous alterations.^{44,45,47,50,70} In addition to the already mentioned GVHD, viral infections, drug eruptions, and secondary mucocutaneous neoplasms, attention should be paid to other infections and less frequent entities. The most common mucocutaneous infections after HSCT are those caused by the varicella-zoster virus, tunnel or catheter exit-site infections, and cutaneous signs of disseminated bacterial or fungal infections. Focal areas of bacterial cellulitis are common in the lower extremities, particularly in the context of edema due to heart failure, lymphedema, or impaired venous return.^{37,38} Molluscum contagiosum and cytomegalovirus infections are also relatively frequent. Of note, these infections may present atypically and more aggressively, given the immunosuppressed state and the polypharmacy in HSCT patients,³⁹ and the possibility of post-transplant lymphoproliferative disorder associated with Epstein–Barr virus, though isolated skin lesions are rare.⁴⁰

Other dermatoses include de novo development of psoriasis,⁴¹ vitiligo in patients without other signs of chronic GVHD,⁴² alopecia in patients without other signs of cGVHD,⁴³ or the appearance of melanocytic nevi in children.⁴⁴ Recently, several cases of dermatomyositis have been reported in patients previously subjected to HSCT, some of them with severe pulmonary involvement,^{45,46} and 1 case of post-HSCT bullous pemphigoid.⁴⁷ A recent study described late cutaneous alterations in children who had undergone HSCT, highlighting a high incidence of vitiligo, psoriasis/sebopsoriasis, alopecia, and nail changes—particularly in children with cGVHD, age < 10 years at the time of HSCT, and with primary immunodeficiency as the underlying condition at transplant.⁴⁸

Discussion

This review presents the main mucocutaneous changes in HSCT recipients. GVHD is the most prominent complication due to its frequency and severity. The acute form poses a complex differential diagnosis—especially vs drug eruptions and viral infections. Accurate diagnosis depends on a thorough clinical history.^{5,8,10} Treatment includes topical/systemic corticosteroids and, more recently, ruxolitinib, approved as second-line therapy.^{15–17} Chronic GVHD is strikingly polymorphic, with more than 10 possible skin signs, including lichenoid and sclerodermiform types, and can also affect oral, genital, hair, or nail sites.^{5,7} This highlights the need for dermatologic evaluation and multidisciplinary care.

Table 4 Main studies evaluating the risk of actinic keratoses and skin cancer after HSCT.

Source	Primary skin cancers (n) or patients with primary skin cancers (n)	Total no. of patients included	Age at HSCT (years), median (range)	Primary diseases	Time to diagnosis (years), median (range)	Cumulative incidence of each specific skin cancer	Identified risk factors
<i>Cutaneous squamous cell carcinoma (cSCC)</i>							
Curtis et al., ⁵³ 2005	19 cSCC	24,011	26.5 (3.5–61.3) (all cSCC cases)	ALL (6), AML (15), CML (14), lymphomas/MM (1), AA (17), FA (4), HGB (1) (all cSCC cases)	7 (0.9–22.9)	1.1% at 20 years	Combination of azathioprine + cyclosporine + steroids (all cSCC cases); azathioprine-containing therapies; long-term immunosuppression; chronic GVHD
Hasegawa et al., ⁵⁴ 2005	4 cSCC	557	33.6	CML (2), NHL (1), AA (1)	4.37	ND	ND
Leisenring et al., ⁵⁵ 2006	53 cSCC (includes mucosal)	211	41.6 (6.8–71.4) (skin and mucosal SCC)	Hematological/marrow failure (10), malignant hematological disease (84), other malignant neoplasms (1) (skin and mucosal SCC)	6.3 (0.3–24.8)	3.5% at 20 years	Acute GVHD, chronic GVHD, younger age at transplant (<10 years)
Gallagher and Forrest ⁵⁵ , 2007	4 cSCC	926	49	CML (1), AML (1), MDS (1), NHL (1)	2.1	ND	ND
Rizzo et al., ²⁹ 2009	19 cSCC	28,874	ND	ND	ND	ND	Chronic GVHD, male sex
Yokota et al., ³² 2012	1 cSCC	2062	46	CML	1.6	ND	ND
Wojenski et al., ⁵⁷ 2015	27 cSCC	381	55 (39–71)	Most common were AML (7), CLL (9), and MDS (6)	ND	19% at 5 years	Male gender, underlying primary malignancy of CLL, transplant age, pre-HSCT skin cancer, extracorporeal photopheresis, UV therapy

Table 4 (Continued)

Source	Primary skin cancers (n) or patients with primary skin cancers (n)	Total no. of patients included	Age at HSCT (years), median (range)	Primary diseases	Time to diagnosis (years), median (range)	Cumulative incidence of each specific skin cancer	Identified risk factors
Lupo-Stanghellini et al., ⁵² 2016	6 cSCC	302	ND	ND	3.5 (0.9–20) (both cSCC and BCC)	3.2% at 3 years and 6.2% at 5 years (both cSCC and BCC)	Voriconazole
Omland et al., ⁵⁸ 2016	4 cSCC (2 allogeneic HSCT and 2 autologous HSCT)	3302	ND	ND	ND	ND	ND
Kuklinski et al., ⁵⁰ 2017	78 cSCC	2638	ND	ND	ND	ND	Chronic GVHD, male sex, voriconazole
Tanaka et al., ⁵⁹ 2017	4 (all oral squamous cell carcinomas)	1060	ND	ND	ND	24.8% at 2 years (all oral cases)	ND
Wu et al., ⁶⁰ 2019	79 cSCC	1974	58.1	AML, ALL, CML, CLL, lymphomas, others	ND	IRR, 9.8; 95%CI, 7.7–12.3	Age, CLL, chronic GVHD
Scott et al., ⁶¹ 2020	62 cSCC	872	ND	AML, MPD, ALL, CLL, plasma cell disorders, CML, lymphomas, other non-malignant disorders	ND	12.3% at 5 years; 95% CI, 8.5–16.3	Chronic GVHD, Fitzpatrick skin type I
<i>Cutaneous squamous cell carcinoma (cSCC)</i>							
Gruber et al., ⁶² 2024	17 cSCC (includes 3 oral and 1 genital)	266	ND	AML	ND	4.2% [95% CI (2.2, 7.2)] and 8.1% [95% CI (4.6, 12.8)] at 10 and 15 years, respectively	ND

Table 4 (Continued)

Source	Primary skin cancers (n) or patients with primary skin cancers (n)	Total no. of patients included	Age at HSCT (years), median (range)	Primary diseases	Time to diagnosis (years), median (range)	Cumulative incidence of each specific skin cancer	Identified risk factors
<i>Squamous cell carcinoma in situ (SCCis)</i>							
Gruber et al., ⁶² 2024	8 (includes 1 genital)	266	ND	AML	ND	ND	ND
<i>Basal cell carcinoma (BCC)</i>							
Hasegawa et al., ⁵⁴ 2005	5 BCC	557	39.8	ALL (2), CML (2), NHL (1)	7.3	ND	ND
Leisenring et al., ⁵⁵ 2006	201 BCC	211	38.1 (2.9–71.3)	Hematological/ marrow failure (7), hematological cancer (150), other malignant neoplasms (1)	7.9 (0.5–30.2)	6.5% at 20 years	TBI, fair skin color, chronic GVHD, younger age at transplant (< 10 years), leukemia/ lymphomas/ blood or malignant bone marrow disease as primary diagnosis
<i>Basal cell carcinoma (BCC)</i>							
Gallagher and Forrest, ⁵⁶ 2007	8 BCC	926	41	CML (3), ALL (1), AML (1), MDS (1), MM (1), NHL (1)	7.6	ND	ND
Borgmann et al., ⁶³ 2008	1 BCC	490	7.8	ALL	20.3	ND	ND
Schwartz et al., ⁶⁴ 2009	282 BCC	6306	ND	ND	ND	ND	TBI with higher risk for younger ages (< 10 years) at transplant and no excess risk for ages > 40 years at transplant, fair skin color for patients who had not undergone TBI, chronic GVHD in patients without TBI

Table 4 (Continued)

Source	Primary skin cancers (n) or patients with primary skin cancers (n)	Total no. of patients included	Age at HSCT (years), median (range)	Primary diseases	Time to diagnosis (years), median (range)	Cumulative incidence of each specific skin cancer	Identified risk factors
Yokota et al., ³² 2012	3 BCC	2062	40 (17–50)	AML (2), ALL (1)	8.4 (7.1–17.6)	ND	ND
Lupo-Stanghellini et al., ⁵² 2016	19 BCC	302	ND	ND	3.5 (0.9–20) (both cSCC and BCC)	3.2% at 3 years and 6.2% at 5 years (both cSCC and BCC)	ND
Omland et al., ⁵⁸ 2016	24 BCC (7 allogeneic HSCT and 17 autologous HSCT)	3302	ND	ND	ND	ND	ND
Kuklinski et al., ⁵⁰ 2017	35 BCC	2638	ND	ND	ND	ND	Chronic GVHD, male sex, voriconazole
Wu et al., ⁶⁰ 2019	54 BCC	1974	54.5	AML, ALL, CML, CLL, lymphomas, others	ND	IRR, 2.5; 95%CI, 1.9–3.2	CLL, reduced-intensity conditioning, acute GVHD, chronic GVHD
<i>Basal cell carcinoma (BCC)</i>							
Scott et al., ⁶¹ 2020	62 BCC	872	ND	AML, MPD, ALL, CLL, plasma cell disorders, CML, lymphomas, other non-malignant disorders	ND	9.1% at 5 years; 95% CI, 5.4–12.8	Age, phototherapy exposure prior to allogeneic HSCT

Table 4 (Continued)

Source	Primary skin cancers (n) or patients with primary skin cancers (n)	Total no. of patients included	Age at HSCT (years), median (range)	Primary diseases	Time to diagnosis (years), median (range)	Cumulative incidence of each specific skin cancer	Identified risk factors
<i>Melanoma</i>							
Baker et al., ⁶⁵ 2003	8 melanomas	3372	ND	ND	ND	O:E, 8:0.96, SIR, 8.3 (95% CI, 3.6–15.1), SIR, 6.7	ND
Curtis et al., ⁵³ 2005	22 melanomas	24,011	ND	ND	ND	ND	ND
Brown et al., ⁶⁶ 2005	5 melanomas	605	ND	ND	North (O:3, 5:0.85)	ND	ND
Rizzo et al., ²⁹ 2009	18 melanomas	28,874	ND	ND	1-to-4 year group (< 1 to > 10 years)	O:E ratio, 3.47, SIR, 1.5	T-cell depletion, TBI, short latency period (< 1 year), female sex
Yokota et al., ³² 2012	1 melanoma	2062	51	NHL	2.1	ND	ND
Mahindra et al., ⁶⁷ 2015	19 melanomas	4161	ND	ND	SIR 3.58 (CI, 1.82–6.29)	ND	ND
Omland et al., ⁵⁸ 2016	6 melanomas (2 allogeneic HSCT and 4 autologous HSCT)	3302	ND	ND	ND	ND	ND
Tanaka et al., ⁵⁹ 2017	1 melanoma	1060	ND	ND	ND	ND	ND
Wu et al., ⁶⁰ 2019	11 melanomas	1974	48.6	AML, ALL, CML, CLL, lymphomas, others	ND	IRR, 3.3; 95%CI, 1.7–5.9	None

Source: Adapted from the authors' original work.

AA: aplastic anemia; FA: fanconi anemia; ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; BCC: basal cell carcinoma; CI: confidence interval; CLL: chronic lymphatic leukemia; CML: chronic myeloid leukemia; cSCC: cutaneous squamous cell carcinoma; GVHD: graft-versus-host disease; HGB: hemoglobinopathies; HSCT: hematopoietic stem cell transplantation; IRR: incidence rate ratio; MDS: myelodysplastic syndrome; MM: multiple myeloma; MPD: myeloproliferative disorder; ND: not described; NHL: non-hodgkin lymphomas; SIR: standardized incidence ratio; TBI: total body irradiation.

Table 5 Main Studies Evaluating Mucocutaneous Alterations (Other than GVHD) After HSCT.

Author/year	Sample size	Study type and conditions evaluated	Results
Canninga-van Dijk et al. ³⁷ , 2003	ND	Narrative review - All types of indications	Patients undergoing HSCT, in addition to viral rashes, are at higher risk of bacterial infections (especially <i>Staphylococcus aureus</i> pyoderma), herpes simplex and varicella-zoster virus infections, cytomegalovirus reactivation, molluscum contagiosum, or fungal infections. - Their presentation can be atypical and more aggressive given the context. - Of note, the possibility of EBV-associated post-transplant lymphoma, although presentation with isolated cutaneous lesions is rare.
Mabuchi et al. ⁴¹ , 2012	1	Isolated case report - Single-center - NHL	Psoriasis can develop de novo after HSCT from a non-psoriatic donor.^a In this case, 10 years after allogeneic HSCT in a patient with NHL.
Khalil et al. ⁶⁸ , 2014	92	Retrospective cohort study - Single-center - Non-malignant diseases	Six patients (6.5%) were diagnosed with vitiligo unrelated to chronic GVHD, 6 (6.5%) with autoimmune hemolytic anemia, 6 (6.5%) with idiopathic thrombocytopenia, 3 (3.3%) with mild leukopenia, 2 (2.2%) with aplastic anemia, and one (1.1%) with autoimmune thyroid disease. - Autoimmune complications were more frequent in patients who underwent HSCT for metabolic disorders.
Kato et al. ⁴⁷ , 2015	1	Isolated case report - Single-center - T-cell Lymphoblastic leukemia	HSCT could be a risk factor for bullous pemphigoid in patients undergoing HSCT. Therefore, in cases of suspicious clinical presentation, it should be ruled out with clinical examination, biopsy, and serology for anti-epidermal basement membrane antibodies.
Bae et al. ⁴² , 2016	2457 HSCT recipients vs 8241 controls	Retrospective cohort study - Multi-center - All diagnoses	- An association with vitiligo was found in HSCT patients, independently of the presence of GVHD and higher than in the control group. - The risk factors most associated with the development of vitiligo were allogeneic HSCT and bone marrow as the source.

Table 5 (Continued)

Author/year	Sample size	Study type and conditions evaluated	Results
Song et al. ⁴⁴ , 2017	85 HSCT recipients vs 85 controls	Prospective cohort study - Single-center - All diagnoses	- Children who underwent HSCT had significantly more nevi than controls (median [range]: 44 (0–150) vs. 11 (0–94), $p=0.0001$). - Children with HSCT had significantly more nevi > 5 mm in diameter and more atypical nevi than controls. - Factors associated with a higher number of nevi included malignant indication for HSCT, pre-transplant chemo, TBI exposure, and myeloablative conditioning. - The percentage of permanent alopecia was 15.6% (41/263 patients). - A conditioning regimen with busulfan and busulfan plus fludarabine (OR, 5.7 [CI, 2.5–12.7] and OR; 7.4 [CI, 3.3–16.2], respectively) was the main risk factor and was associated with alopecia regardless on the presence of acute/chronic GVHD.
Bresters et al. ⁴³ , 2017	263	Retrospective cohort study - Single-center - All diagnoses	- 14% ($n=12$) of patients developed vitiligo; 16% ($n=14$) developed psoriasis/sebopsoriasis; 25% ($n=21$) developed alopecia; and 6% ($n=5$) developed nail alterations. - Factors significantly associated with vitiligo, independent of GVHD, included an indication of primary immunodeficiency and younger age at transplant (<10 years). - Factors significantly associated with alopecia, independent of GVHD, were busulfan conditioning and a family history of early-onset androgenic alopecia. - The only risk factor identified for nail alterations was a history of chronic GVHD.
Huang et al. ⁴⁸ , 2018	85	Retrospective cohort study - Single-center - All diagnoses	- 14% ($n=12$) of patients developed vitiligo; 16% ($n=14$) developed psoriasis/sebopsoriasis; 25% ($n=21$) developed alopecia; and 6% ($n=5$) developed nail alterations. - Factors significantly associated with vitiligo, independent of GVHD, included an indication of primary immunodeficiency and younger age at transplant (<10 years). - Factors significantly associated with alopecia, independent of GVHD, were busulfan conditioning and a family history of early-onset androgenic alopecia. - The only risk factor identified for nail alterations was a history of chronic GVHD.
Miyagi et al. ⁴⁵ , 2023	2	- Two case reports and literature review - Single-center	- Dermatomyositis can be a late complication of HSCT, and it's essential to rule it out in patients undergoing HSCT who present with compatible cutaneous and muscular symptoms.

GVHD: graft-versus-host disease; CI: confidence interval; NHL: non-hodgkin lymphoma; ND: not described; OR: odds ratio; Chemo: chemotherapy; TBI: total body irradiation; HSCT: hematopoietic stem cell transplantation.

^a Previously, 2 cases of psoriasis after HSCT had been described in patients who received a transplant from a psoriatic donor.

Conclusions

HSCT has revolutionized the treatment of various hematologic and non-hematologic diseases but carries a significant risk of mucocutaneous complications. Among them, GVHD—acute and chronic—remains a major diagnostic and therapeutic challenge. Other frequent issues include skin infections and drug eruptions. Early identification and a multidisciplinary approach are essential for improving quality of life and long-term outcomes. Skin cancer screening and photoprotection advice are also recommended, especially in at-risk individuals.

Conflicts of interest

None declared.

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